

Exploring exposure in vivo in chronic pain

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Chapter 7

Summary and general discussion

When traditional and biomedical treatments fail and pain-related disability grows, pain patients are often referred to rehabilitation centers. Generally, the treatment in these centers is interdisciplinary and based on bio-psychosocial or behavioral rehabilitation models which assume that pain disability is not only determined by the underlying pathology, but also, by cognitive, behavioral, emotional and social factors. Treatment methods from operant conditioning principles and psychophysiological and cognitive psychology concepts are applied to the treatment of chronic pain. Research shows variable results of cognitive-behavioral treatment programs. As a result, it is argued to match treatments to patient characteristics to increase the effectiveness of treatments (Turk, 1990). To develop effective customized treatments, in recent years behavioral pain research is focused on the mechanisms by which patients with acute pain become chronically disabled. A number of studies have reported that pain-related fear is one of the strongest predictors of variation in physical performance (Vlaeyen & Linton, 2000).

Because of its substantial contribution of in the maintenance of chronic pain, pain-related fear is an important target for intervention. Indeed, several studies revealed that exposure in vivo (GEXP) is an effective treatment in chronic low back pain patients who report high levels of pain-related fear. However, on the basis of the results of these studies and the overall complexity of exposure there are still several questions that need to be addressed. For example, which treatment characteristics make the GEXP successful or unsuccessful in pain-related fear? What is actually learned during GEXP? Does the extinction of pain-related fear generalize to other movements and activities that were not included in the treatment? Is GEXP applicable in patients with pain disorders with observable tissue pathology such as neuropathic pain? In short, enough questions to answer in the process of optimizing GEXP in pain-related fear. By examining whether the effects of GEXP generalized from chronic low back pain to other pain problems such as complex regional pain syndrome and posttraumatic neck pain, the contribution of specific treatment components to outcome, and the question whether exposure to multiple stimuli enhances generalization after treatment, the goal of this dissertation was to further explore the utility of GEXP.

Before discussing the results, the main findings can be summarized as follows. The first study (chapter 2) focused on the role of pain-related fear in Complex Regional Pain Syndrome type I (CRPS-I). The results showed that pain-related fears, if measured with the PHODA, as well as pain severity were important predictors of pain disability. Although replications are necessary, the conclusion that pain-related fear in CRPS-I patients is a promising research direction in the understanding of pain disability in CRPS appeared justified. Chapters 3 and 4 described a number of single-case experiments in which the effectiveness of GEXP in patients with posttraumatic

neck pain (PTNP) and CRPS-I reporting substantial pain-related fear was tested. Both studies supported the effectiveness of a GEXP approach in these patients. GEXP was successful in decreasing not only pain-related fear, but also pain intensity, disability levels, and in increasing the daily physical activity level. Striking was also that physiological signs and symptoms related to CRPS-I were positively influenced by GEXP.

The reduction of pain-related fear occurred rather quickly after the initiation of the exposure treatment. As the exposure protocol used in the aforementioned studies always started with an educational part, the results might have been the result of the new information provided by the therapist during this initial session. Therefore, a study was carried out (Chapter 5) in which we examined the contribution of the educational part of GEXP in the reduction of pain-related fears and cognitions, and the associated disability and physical activity. The results showed that pain-related fears and cognitions were indeed positively influenced by the education. Contrary, performance measures of daily activities were not affected by the educational sessions and improved only during the exposure sessions. Finally, in chapter 6 it was examined whether the effects of GEXP in fearful CRPS-I patients generalized to threatening activities which were not addressed during GEXP. Overall, it seems that, irrespective of the kind of exposure, GEXP generalized to new threatening activities.

Testing the role of pain-related fear in complex regional pain syndrome

In recent years the investigation into potential pathophysiological mechanisms involved in Complex Regional Pain Syndrome type I (CRPS-I) has intensified. The general consensus is that the pathophysiology of CRPS-I is still not known (Wilson et al., 2005), and the contribution of psycho-physiological interactions to the development of CRPS-I is largely speculative. Although it has repeatedly been shown that in chronic musculoskeletal pain pain-related fear is associated with escape-avoidance behaviors and associated functional disability, the role of pain-related fear in CRPS-I was never tested systematically. Recently, Moseley et al. (2008) demonstrated that motor imagery increased pain and swelling in CRPS-I patients and that this effect seems to be modulated by pain catastrophizing and pain-related fear. According to the authors, these results corroborate the findings from recent studies that highlight the contribution of cortical mechanisms to pain on movement in CRPS-I which was suggested earlier (Andersen & Buneo, 2003; Gieteling et al., 2008; Krause et al., 2006; Maihöfner et al., 2005, 2007; Schwenkreis et al., 2003). During movement, patients with chronic pain show more activation of the right insular cortex (Maihöfner et al., 2007) thought to hold representations of the sympathetic nervous system (Hilz et al., 2006). The increase in swelling related to pain-related fear and pain

catastrophizing suggests that cognitive variables may modulate the link between motor and sympathetic activities.

Is pain-related fear an important predictor of general physical health and functional disability in CRPS-I?

Pain-related fear is one of the strongest predictors of disability in chronic musculoskeletal pain and pain-related fear appears relevant CRPS-I as well. Therefore, we investigated the role of pain-related fear in CRPS-I using data of two cross-sectional studies (chapter 2). Study I included CRPS-I patients visiting an outpatient pain clinic. In study II, members of the Dutch association for CRPS-I patients were invited to complete a number of questionnaires. Overall, both studies showed that pain severity was an important predictor of general physical health and a higher level of functional disability respectively. Additionally, study I revealed a significant relationship between depression and general physical health. An interesting, and somewhat unexpected finding was that pain-related fear was an important predictor of functional disability in CRPS-I, but only when measured with a pictorial fear of activity scale (PHODA; Dubbers et al., 2003; Jelinek et al., 2003) -as was the case in study II- and not when measured with a more commonly used questionnaire tapping fear of movement/(re)injury (TSK, Miller et al., 1991). There are at least two explanations for this unexpected finding. One possible explanation for this could be that the PHODA, as opposed to the TSK, is more sensitive and better capable to capture inter-individual variation. The results show that the standard deviation of the mean TSK score is much smaller than that of the mean PHODA score. This means that it would be possible to infer that the patients have indicated that they believe pain due to movement is a sign of impending harm (TSK), but there is more individual variation in the kind of activities that are considered harmful (PHODA). Indeed, the PHODA was developed as a specific measure of pain-related fear, including pictorial presentations of concrete movements that are relevant for patients with upper and lower extremity pain. Conversely, the TSK is made up of statements reflecting the idea that painful movement in general is harmful. Since the PHODA requires patients to respond to specific pictorial stimuli reflecting movements of the upper or lower extremities, it has also the potential to activate fear schemata more directly and elicit emotional reactions. The importance of the immediate and specificity of fear provoking stimuli has been noted by several studies. For example, Lang (1995) showed reliable affective psychophysiologic responses, defined by the judged valence (appetitive/pleasant or aversive/unpleasant) and arousal elicited by a threatening pictures. Picture-evoked affective responses are also associated with potentiated startle reflexes during unpleasant pictures and inhibited startle reflexes during the presentation of pleasant pictures. In addition, both effects were augmented by

high picture arousal. Also Wessa et al. (2005) showed in a group of motor vehicle accident survivors with subclinical posttraumatic stress disorder (PTSD) that accident-related pictures enhanced startle responses and neutral pictures had a significantly lower response. The authors suggest that traumatized persons with PTSD show exaggerated emotional responses to trauma-related stimuli and reduced cognitive responses to several types of stimuli that may interfere with the extinction of the emotional trauma memory. It would be interesting to study psychophysiological responses of CRPS patients when exposed to the PHODA pictures. Another explanation is that PHODA measures expected pain level fear of pain in certain contexts. Contrary to the findings in patients with low back and cervical pain (e.g. Vlaeyen & Linton, 2000; Nederhand et al., 2006), clinical experience suggests that CRPS-I patients describe their fear not in terms of movement and injury, as tapped with the TSK, but in terms of uncontrollable interoceptive stimuli (e.g. pain). Previous research (e.g. Asmundson & Nicholas-Carleton, 2005; Keogh et al., 2001; Carleton et al., 2006) has shown that fear of pain, as measured with PASS, increases vulnerability to pain disability. However, as far as known, it is never examined whether fear of pain is related to CRPS-I. An intriguing question is whether pain-related fear in neuropathic pain has different features than in musculoskeletal pain, or more specifically what the exact conditioned stimulus is. It might well be that in CRPS patients aversive interoceptive stimuli are more important than proprioceptive ones which may be more relevant to chronic back pain patients.

Exposure in patients with Posttraumatic Neck Pain and Complex Regional Pain Syndrome type I reporting substantial pain-related fear

Overall, the general understanding is that Posttraumatic Neck Pain (PTNP) and Complex Regional Pain Syndrome type I (CRPS-I) are complex in nature and that the number of empirically supported treatments for these pain disorders remains limited. Nevertheless, in chronic pain management there is increasing consensus regarding the importance of a behavioral medicine approach to symptoms and disability. For patients with PTNP, cognitive behavior therapy (CBT) programs have been developed as well, of which those promoting physical activity and are focussed on regaining function have proven to be relatively more effective (Hurwitz et al., 2008). Although these studies suggest that activity increase is associated with faster return to work and a decrease in pain and disability levels, there is evidence showing that these changes are mediated by the reduction of the catastrophic (mis)interpretations of pain (Smeets et al., 2006, Leeuw et al., 2008, Spinhoven et al., 2004). In CRPS-I functional restoration and reactivation via interdisciplinary approach have been thought to be required for optimal outcome (Harden, 2005). However, the specifics as to what the components of an effective, efficient functional restoration

program should be, what modalities are to be delivered, when, and for how long were all open questions.

Given the beneficial results of GEXP in CLBP patients who report high levels of pain-related fear, and because pain-related fear has shown to be associated with PTNP and CRPS-I, there are good reasons to believe that a GEXP treatment would be beneficial for fearful PTNP and CRPS-I patients as well. For the majority of these patients explanations grounded in physical pathology are inadequate and conventional approaches to pain have failed, which suggest that alternative explanations need to be explored. Patterns of pain-related avoidance behaviour seen among these patients can be individually analyzed using an associative fear learning framework and subsequently targeted with exposure-based treatments. From this perspective, the mechanism of action for successful treatments in fearful PTNP and CRPS-I patients is based on a frequent and gradual increase of pain-eliciting stimuli without trying to reduce or alter the experience. Indeed, the exposure to movements might correct the sustained mismatch between motor activity and sensory feedback in PTNP and CRPS-I patients (e.g. Harden, 2005, Nijs et al., 2009), which may serve as ongoing source of nociception. The incorporation of GEXP as therapeutic approach for functional restoration is then axiomatic, but should be confirmed.

Does GEXP extend to PTNP and CRPS-I patients?

To answer this question, two intervention studies were conducted. The current studies supported a GEXP approach to chronic PTNP (study I) and CRPS-I (study II) patients reporting elevated levels of pain-related fear. The GEXP was successful, and as shown in study I, superior to GA in decreasing levels of pain-related fear, pain catastrophizing, pain disability, and pain intensity. In the same study also improvements were found in the performance of physical activity in the home situation as measured with ambulatory activity monitors. A remarkable finding was that the participants of Study II reported that they did not experience any physiological signs and symptoms anymore after GEXP and even at 6 months. However, it is not clear how GEXP might address either of these processes. One possible explanation is that GEXP is a strategy mechanism that impacts higher order motor processes such as motor intent or motor planning. Another explanation might be that GEXP focused on mental and visual attention in order to move the affected extremity. Thus, perhaps GEXP requires the patient to attend to the affected extremity, which may serve to reverse a learned disuse of the affected extremity (Butler, 2001).

Despite the success of GEXP several limitations of these replicated single case experimental studies should be mentioned. *First*, the preliminary results reported are

limited in that they are based on a small number of patients. However, in both studies an experimental design was chosen with appropriate statistical analyses (randomization tests). Randomization tests have the advantage of being valid for single-case experiments without making distributional assumptions, of being easy to apply, and of being extremely versatile for even the most complex single-case designs (e.g. Onghena & Edgington, 2005). Conversely, the results of the non-daily measures, with limited number of data points, were not subjected to randomization tests and for the most part based on arbitrarily chosen preset-criteria. *Second*, only in study I GEXP was compared to another intervention. Because the experimental design did not include washout periods between the different treatment components – for evident reasons-, it is possible that carry-over effects occurred. Indeed, when GA followed GEXP the improvements remained stable, which is also consistent with the favourable FU results. As already noted, GA showed to be helpful for chronic neck pain disability across a number of studies. However, in study I, change during GA was marginal at best, when GA preceded GEXP. Both GA and GEXP were performed according to a specific protocol. In addition, GA and GEXP were delivered by different therapists. Because patients' attitudes and beliefs, and thereby patients' disability levels, may be derived from the projected attitudes and beliefs of health care providers (e.g. Rainville, 1990), the two teams were comparable in terms of experience and therapists' preferences. Efforts were made to achieve the same level of enthusiasm in each therapist who participated in either GA or GEXP. Nevertheless, therapists may consider GEXP as a more credible treatment than GA which may have influenced their treatment behaviour in favour of GEXP (e.g. Leeuw et al., 2008). *Third*, study II was impeded by the use of self-report measures only, which may have been subject to response bias. *Finally*, the 6-month FU may not have been sufficient to determine the long-term effect of GEXP or long-term quality of life. To increase generalization of GEXP across patients more simultaneous or sequential replications of single-case experiments with future measurement occasions are needed. Replication strategies also allow one to design small clinical trials, detect patterns of response or subgroup of patients or design Randomized Clinical Trials (RCT) as a collection of replicated single-case experiments. Further, physiological measures (e.g. pain thresholds, oedema and thermal detection) or objective measures of behavior seem most promising as target measures in single-case experiments for pain research.

How many exposure sessions are needed to demonstrate trend changes and significant effects?

GEXP has already successfully been applied in chronic low back pain (CLBP) patients. Not only a number of single-case experimental studies have been carried out successfully, also randomized controlled clinical trials have shown positive results with regard to pain disability and pain-related fear (Leeuw et al., 2008; Linton et al., 2008; Woods & Asmundson, 2008). However, in comparison with the single-case experimental exposure studies in patients with low back pain of Vlaeyen et al. (2001; 2002a; 2002b) the current studies showed that more exposure sessions were needed to demonstrate trend changes and significant effects in PTNP and CRPS-I patients. A possible explanation is that PTNP and CRPS-I patients experience multiple complaints and fears, not just fear of movement. Not only neck pain but also symptoms such as headache, visual disturbances, dizziness, weakness, paraesthesia, nausea, both upper and lower limb numbness and tingling, tinnitus, and cognitive problems (concentration and memory disturbances) are common in PTNP patients in the acute stage after a traumatic event (Barnsley et al., 1994; Ferrari et al., 2005). Symptoms of CRPS-I can also include abnormal swelling, abnormal hair or nail growth, abnormal skin color or temperature changes, abnormal sweating, limited range of motion and movement disorders (Wilson et al., 2005). Although pain is normally a leading symptom in CRPS-I, the autonomic, motor, and trophic signs and symptoms of CRPS-I are not necessarily coupled with pain (Eisenberg & Melamed, 2003). In many patients with CLBP, the main concern is the experienced pain interfering with daily life activities signals injury. These concerns can relatively easily be challenged as injury will never follow increased physical activity, given the non-specificity of their pain complaints. In contrast, the concerns of PTNP patients (e.g. "If I would lift heavy weights, then I do not have full control of my neck, which will worsen the pain complaints, with the result that I will not be able to do my job in the future") and CRPS-I patients (e.g. "If I would walk without crutches, the pain will worsen and the foot becomes thick and intensely hot, by which I will loss control of my leg, which increased the likelihood of uncontrolled movements, which will aggravate the CRPS") may be much more difficult to challenge. Another explanation of the delayed effect could be that, contrary to GEXP in CLBP, the sessions mainly consisted of exposure to personally relevant activities that represented the main functional goals that were chosen by the patients themselves occurred in a later phase. Because of the multiple fears in PTNP and CRPS-I patients, the progress in the fear hierarchy occurred more slowly than during GEXP in CLBP.

In CRPS-I patients it is possible that the observed peripheral changes of CRPS-I mediated the effect of information on pain. This assumption is supported by a study of Arntz and Claassens (2004) who tested whether the meaning attached to pain influ-

ences the pain intensity. By suggesting that a very cold metal bar which was briefly placed in the neck was either hot or cold, the potentially harmful property of the stimulus was experimentally manipulated. Participants who were given the information that the metal bar was hot reported more pain than those who were told that a cold bar was applied to their neck. The authors found that harm beliefs are a crucial aspect of meaning that mediated the association between the information and provided report of pain. Based on these findings it seems interesting to investigate whether there is a difference between CRPS-I patients who experience there vasomotor abnormalities in the affected extremity as warm or those who experience them as cold. In CLBP patients, possible tissue-damage is not observable, by which it might be easier to modify their meaning attached to their pain as compared to CRPS-I patients in whom symptoms are clearly visible. Additionally, these observable symptoms might be interpreted catastrophically and may direct hypervigilance to sensations of the body, thereby amplifying the pain experience. Indeed, there is evidence that the intensity of pain is related to this vigilance (e.g. Crombez et al., 2004). In line with this the catastrophic interpretation of pain might include anxiety, which in turn might amplify pain intensity (Arntz et al., 1991; 1994; Arntz & de Jong, 1993).

Mediating effect of GEXP

According to the single-case studies of Vlaeyen et al. (2001; 2002a; 2002b) it is of interest that not only pain-related fear, pain catastrophizing and pain disability but also pain experience is positively affected by GEXP. Moreover, the results suggest that the decrease in pain experience temporarily follows an associated decrease in pain-related fear. This is in line with the Fear-Avoidance model. However, such strong reduction in pain is not common in usual cognitive-behavioral treatments for chronic pain (Kole-Snijders et al., 1999; Morley et al., 1999). Furthermore, it is remarkable that in study II self-reported trophic changes or enhanced efficacy of nociceptive mechanism or cortical changes are influenced by GEXP. We offer five possible explanations for these findings.

First, one explanation is that change in pain and autonomic, motor, and trophic signs and symptoms of CRPS-I are related to pain catastrophizing and pain-related fear which are the primary focus of GEXP. Indeed, Moseley et al. (2008) found in patients with CRPS-I and also in a group of non-CRPS pain that the higher patients report pain-related fear or pain catastrophizing, the larger the increase in pain and swelling with imagined hand movements. Sympathetic arousal is positively related to an increase of swelling. Maihöfner et al. (2007) showed that during movement chronic pain patients have more activation of the primary insular cortex, thought to hold representations of the sympathetic nervous system, than healthy controls. The

findings that increase in swelling are related to pain-related fear and pain catastrophizing suggests that cognitive variables may modulate the link between motor and sympathetic activities. The results of Moseley et al. (2008) suggest that pain-related fear affects motor processes and pain even in the absence of actual performance of physical movement, also demonstrating that cognitions may modulate pain processing in the absence of nociception.

Second, it is demonstrated that some chronic pain patients have an involuntary neurological neglect-like condition (Galer & Jensen, 1999; Förderreuther et al., 2004; Frettlöh et al., 2006). This finding suggest that PTNP and CRPS-I patients may experience a change in their body perception which can be very unsettling, frightening and/or repulsive, and ensures avoidance behavior. Therefore, for the patients it could be difficult to maintain conscious attention to the affected limb and its adequate use, which will consequently worsen the disordered sensorimotor function. Thus, the success of GEXP may be due to requiring to attend to the affected extremity for a certain time. In which case, GEXP may simply serve to reverse a learned experiential avoidance response of the affected extremity or limb.

Third, the reduction of pain-related fear levels may be due to a reduction of selective attention towards the affected body extremity. Experimental studies on the role of attention and pain-related fear have shown that chronic pain patients with elevated levels of pain-related fear habitually attend to somatic sensations (Asmundson et al., 1997; Peters et al., 2002). These findings suggest the decrease in pain experience during GEXP was mediated by a process in which the reduction of the threat value of previously fear-eliciting stimuli also produced a redirection of the attention away from pain and bodily sensations.

Fourth, the effects of GEXP could also be mediated by an increase in acceptance of pain. For example, Wicksell et al. (2008) tested an intervention consisted of values-based exposure and acceptance strategies to improve functioning and life satisfaction by increasing the participants' abilities to behave in accordance with values in the presence of interfering pain and distress (psychological flexibility). In this study, the functional relationship between chronic pain and disability was explained by a learning theory model emphasizing avoidance of unpleasant experiences (e.g. pain, fatigue, fear; Fordyce, 1976). For chronic pain patients activities that reduce pain and distress but are less active and stimulating will likely produce a reinforcing short-term relief. Over time, this behavior may gradually compromise functioning and life quality without a corresponding decrease in symptoms. Exposure to previously avoided situations is considered to be the core intervention, emphasizing acceptance of what cannot be directly changed (thoughts, emotions, bodily sensations) as a way of engaging in activities that are meaningful but possibly painful or

fear-provoking. Behavioral activation was not carried out during sessions but rather by the patients between sessions. The goal of acceptance and commitment therapy (ACT), is to increase psychological flexibility, defined as the ability to act effectively in accordance with personal values in the presence of negative private experiences such as pain or distress (Hayes et al., 2006). Compared to a wait-list control condition Wicksell et al. (2008) showed that after the exposure-ACT condition for pain disability, life satisfaction, fear of movements, depression and psychological inflexibility significant differences in favour of the treatment group were seen. For both groups no change was seen in pain intensity, which implies that reported increase in functional ability and life quality was not due to a corresponding decrease in pain. Based on these results and because GEXP differs from the exposure strategies as applied by Wicksell et al. (2008), future GEXP studies may test the validity of the idea that the results are mediated by increased acceptance.

Fifth, in the literature on catastrophizing's influence on pain in the context of rheumatic disease (RA) it is suggested that pain catastrophizing might be directly or indirectly associated with inflammatory processes (Edwards et al., 2006). For example, Schoenfeld-Smith et al. (1996) have reported positive relationships between catastrophizing (or helplessness, one component of catastrophizing) and elevated indices of disease activity and inflammation. Because studies in RA have shown that high levels of catastrophizing prospectively predicted worsening erythrocyte sedimentation rates (e.g. Evers et al., 2003), these authors suggest directional relationships between pain catastrophizing and inflammation. Catastrophizing may also contribute to interactions between pain and the immune system (Watkins & Maier, 2002). In sum, although no blood samples were taken from our patients, one could speculate that effects of GEXP might be mediated by a reduction of pro-inflammatory cytokines associated with a reduction of pain catastrophizing.

GEXP initially increases pain levels

Despite the overall positive influence of GEXP on pain experience both in study I and II there appears to be an increase in pain experience at the onset of GEXP. In the PTNP-study a possible explanation may have to do with the natural history of the participants. They could be characterized as not-at-fault drivers who experience feelings of anger at the other driver who caused the injury and keeping him/her from attaining an important life goals (Ferrari et al., 2005; Mayou, 1994; Berkowitz & Harmon-Jones, 2004). High levels of anger might be associated with more intense pain experience and more severe disability (Bruehl et al., 2003; Burns & Bruehl, 2005). It has been suggested that perceptions of injustice and anger are related. Sullivan et al. (2008) found that individuals who perceived injustice and had sustained injuries in motor vehicle accidents, as a result of someone else's fault, also

reported more severe pain, more pain sites, and greater depression. In addition, DeGood and Kierman (1996) found that chronic pain patients who blamed others for their pain reported more pain and more emotional distress than patients who did not ascribe fault for their pain condition. It is interesting to note that research suggested that blaming others for one's situation appears to be sufficient to engender negative outcomes (Turk & Okifuji, 1996; Blyth et al., 2003) and that perceptions of injustice might allow individuals to remain stuck in their current pain situation. Also subjectively aversive conditions which are the result of the injury can generate anger (Berkowitz & Harmon-Jones, 2004). An example of such aversive conditions could be exposure to activities and/or movements in which physical discomfort or pain will be experienced (Anderson et al., 1998; Berkowitz & Harmon-Jones, 2004). The induction of anger and pain-evoked cardiac responses that are elicited by anger produces increased pain intensity and pain unpleasantness (Rainville et al., 1995). However, there are also studies that have shown the opposite, namely that anger just inhibits pain (e.g. Bruehl et al., 2009). Despite the negative role of anger and perceived injustice on pain experience at the start of GEXP, data from the GEXP study in PTNP (see this thesis) indicate that exposure therapy finally helps reduce the hallmark features of chronic PTNP (e.g. pain experience, disability and fear).

Moderation

Besides the specific effects of exposure it is important to consider the influence of non-specific effects as well. (e.g. Mahomed et al., 2002; Vase et al., 2005; Goffaux et al., 2007). Overall, positive or negative expectations may result in the reduction or amplification of pain along with inhibition or activation of several brain regions (Sawamoto et al., 2000; Porro et al., 2003; Lorenz et al., 2005; Keltner et al., 2006). According to these observations it seems that expectation of either low- or high-intensity painful stimuli has a strong influence on the perceived pain. Clinical studies on the effectiveness of cognitive-behavioral rehabilitation programs for chronic low back pain and fibromyalgia showed that patients' initial beliefs about the success of a given pain treatment have an important influence on the final treatment outcome, and that patients with higher treatment expectancies significantly received less disability compensation, were less fearful and more satisfied (Goossens et al., 2005; Smeets et al., 2008).

A criticism of study I is a lack of consideration for the influence of non-specific effects such as expectation. On the other hand, in study II patients were asked for expectancy and credibility of GEXP. This was done after the educational part of the GEXP, and before the actual exposure. Participants not only received the rationale of the exposure therapy and a positive approach of the diagnosis CRPS-I, a verbal suggestion that clinical improvement should be expected was given as well. Inde-

pendently, both the rehabilitation physician and the other team members told the patients that they may expect a positive influence of GEXP on their pain complaints. The mean expectancy and credibility ratings were relative low for the GEXP in study II. This implied that the patients did not expect that GEXP will help to cope better with their pain complaints, and that they did not believe that GEXP was a meaningful treatment for patients with CRPS-I. However, given the medical history of the CRPS-I patients who have participated in this study, this negative expectancy is hardly surprising. Overall, chronic CRPS-I patients are usually confronted with repeated failures finding a solution for their pain problem. Contrary to be expected, the low expectancy about GEXP did not had any negative effect on the experienced clinical benefits immediately after GEXP and at 6-month FU. All patients did not only report a large decrease in pain disability but also in pain experience and CRPS-I related physiological signs and symptoms.

Finally, effectiveness is not a feature of exposure alone. In the first place, the interactions between patient, therapist and/or therapist team and the exposure sessions and/or therapy program are important for the success of GEXP. For example therapeutic alliance, motivation of the patient, therapist/team prognoses, therapist appraisal of patients behavior, attitude of the therapist (self-confidence, no concern/anxiety when patient bellow with pain) or planning of the sessions are just a few examples which could define the course of the GEXP. As an addition to the ongoing discussion concerning the magnitude of therapist effect in GEXP, therapist variables appear to influence treatment alliance more than outcome (Wampold, 2001).

Contribution of specific treatment components to outcome and generalization of GEXP

Education versus GEXP

The results of the first single-case experimental studies examining the effectiveness of GEXP in patients with chronic low back pain (CLBP) showed abrupt changes in self-reported pain-related fears and cognitions (Vlaeyen et al. 2001, 2002a, 2002b). These changes seem to be more characteristics of insight learning rather than the usual gradual progression of trial and error learning. The educational session at the start of GEXP might have contributed to this insight. To test this hypothesis it was examined in six consecutive CLBP patients, whether a single educational session followed by GEXP or operant graded activity (GA) had indeed a powerful treatment effect. Both daily measures and pre-post assessments showed that after education and the following no-treatment period, subjective ratings of pain-related fears and

catastrophizing decreased substantially. Based on these results it seems that a tailor-made formulation of a patient's pain problem, within a substantive fear-avoidance model, has good empirical support in patient's perceptions about the harmfulness of physical activity and threat value of pain. Moreover, in reducing pain-related fear the results suggest that the education of the current study works in one session which implicates that it would be a really effective intervention to use in primary care if one could identify at-risk patients. Except providing personalized information the aim of the education was also that patients should indicate their adherence to participate in major behavioral change in order to regulate themselves in the period ahead. Adherence implied the patient's active choice in the process, rather than passive co-operation or obedience to the recommendations of the therapist team. Further, it was a process that therapists and patient undertook in order to reach an agreed plan of disability management. Finally, by inviting family or close friends of patients during the educational session the therapist team tried to realize social and emotional support which also appeared to lead to lower levels of anxiety (Edwards & Clarke, 2004).

In addition, the current study has shown that education, although essential, is not sufficient to guarantee that patients actually perform fearful activities and/or movements. Educating the patient that being active leads to functional possibilities alone, and perhaps even a better quality of life, is not enough to make him/her more active. Self-reported performance in daily life, subjective ratings of the PHODA and even activity monitor data support the assumption that GEXP is necessary to modify escape and avoidance behavior due to pain-related fear and not GA. It seems that fearful chronic pain patients can change their behavior by means of exposure therapy. However, motivation to change behavior requires active participation on their part.

A possible reason for the lack of association between beliefs and behavior is that the willingness to perform health-related behaviors involves a complex tangle of attitudes to physical activity, implicit versus explicit affective evaluation, expectations, previous experiences of physical activity, and social pressure. Despite decision alternatives available in memory, decisions often rely on an "attitude-based" strategy, thereby ignoring available and contradictory information (Sanbonmatsu & Fazio, 1990). This means that attitudes such as the deeply ingrained pain-related fear may evoke automatic activation from memory when the patient encounters threatening situations. Explicit attitudes are distinguished from implicit or automatic attitudes and both may guide one's behavior (Fazio, 1990). Explicit attitudes may guide one's behavior by a deliberate and conscious analysis of the costs and benefits of that behavior, whereas implicit attitudes may guide in a more spontaneous and affective manner, without actively considering the positive and negative as-

pects. This means that patients may have different evaluations of the same activity. For example, the patient realizes that his concerns about harm are irrational; however, when suddenly confronted with a threatening movement avoidance of movement will occur all the same. The results of the current study suggest that education did not have a strong effect on patients' implicit attitudes toward pain-related activities or movements but did change their explicit attitudes. It seems that explicit attitudes toward pain-related activities or movements are readily changed when faced with the fear-avoidance model that is inconsistent with the existing propositions about pain. On the other hand, implicit attitudes may change only when new associations are formed through evaluative conditioning or when new propositions ingrain in into new associations (Gawronski & Bodenhausen, 2006). Based on the results it can be assumed that GEXP offers sufficient possibilities for evaluative conditioning processes to change implicit attitudes toward pain-related activities or movements. In addition, because changes of implicit attitudes toward pain-related activities or movements, which are mediated by changes in cognitive strategies (i.e. more positive propositions about pain), may become apparent if there is enough time to ingrain these propositions, it seems that GEXP allows for this possibility.

Generalization

Despite the success of GEXP in chronic pain patients who report high levels of pain-related fear, it is still a question whether fear extinction generalizes to new threatening activities. The results of the activity monitor data of the PTNP-study and the education-study suggests that the confrontation of fear-eliciting activities in the treatment setting is analogue for how patients respond in daily life situations. Moreover, treatment gains produced during GEXP seems to generalize to the home setting and in the absence of therapists. Contrary, some recent experimental studies raise doubt about the generalization of the exposure effects (e.g. Vansteenwegen et al., 2007; Goubert et al., 2005). Research into the return of fear has revealed that extinction does not mean unlearning (e.g. Craske et al., 2008). It appears that the extinguished fear response can arise spontaneously after a while (spontaneous recovery), or reoccur when confronted with a new CS-US event (rapid reacquisition) or an unpredicted US (reinstatement). In addition, it also appears that extinction is context-sensitive (e.g. Craske et al., 2008). It has been established that what has been learned during the process of extinction not necessarily generalizes towards other situations; not even when the extinction process takes place during the original process of acquisition.

Whenever context changes can result in return of fear, the subsequent question is how this return can be prevented and on top of that which typical feature of GEXP is responsible for the supposed generalization. Animal research showed that when-

ever extinction is received in different contexts it leads to less return of conditioned suppression in yet a new context when compared extinction in only one context (Chelonis et al., 1999; Gunther et al., 1998). In human demonstration of multiple context methods as prevention for return of fear is still scarce. By the use of computer-conditioned suppression tasks Neumann (2006) demonstrated that extinction in multiple contexts can reduce renewal of fear. Further, using retrieval cue methods Vansteenwegen et al. (2006) and Collins and Brandon (2002) showed larger return of fear when cues were given that were also present during acquisition than when retrieval cues were also present during extinction. Furthermore, Rowe and Craske (1998) showed that return of fear towards a new spider exemplar was reduced when multiple stimulus examples were used during exposure instead of one and the same spider. Finally, Vansteenwegen et al. 2007 showed that spider-anxious students that were exposed to videotapes with the spider presented in different locations of a house showed less return of fear when confronted with the spider in a new context than students that were exposed to repeated presentations of a videotaped spider in one specific location of the house.

In this thesis a clinical study is described in which the primary objective was to replicate the finding that exposure to multiple conditioned stimuli can enhance the generalization process of extinction. By the use of a randomized replicated single case experimental design it was examined whether GEXP generalized better to a new movement when fearful CRPS-I patients were exposed to 15 activities once as compared to an GEXP program in which fearful CRPS-I patients were exposed to 3 activities to which patients were five time each. In contrast to the expectations, both conditions generalized to new threatening activities. Based on these results it seems that multiple stimuli exposure is not a sine qua non to prevent relapse.

Independent of the context in which certain activities and/or movements will be performed it seems that the experienced pain and even more the catastrophic representation of pain is important in CRPS-I patients. According to the theory of extinction CRPS-I patients learned during GEXP that the US (pain) is less threatening than supposed. The US was, as it were, biased by the representation. In addition, it seems reasonable that the supplemented cognitive techniques during GEXP were necessary to directly challenge negative valence and also the validity of catastrophic assumptions and misinterpretations by which generalization can be realized.

Further, a possible explanation of the success of generalization might be that in both GEXP conditions during each exposure session all patients were exposed to a certain threatening activity which consists of several threatening movements. Moreover, these activities were individually tailored based on a fear hierarchy. It can be assumed that not the variety activities but the repeated exposure to some few indi-

vidually identified threatening activities might be of importance. Another explanation could be that the CS was not the movement or activity, but the painful sensation itself. This may mean that it does not matter which movements or activities are identified, but that exposure to pain and related physiological sensations is sufficient to ensure generalization. In this case, GEXP seems to be a form of interoceptive exposure (e.g. Flink et al., 2009).

Finally, to facilitate generalization it could be important that during GEXP the CS is the same as the CS involved in the acquisition of the fear responses. GEXP was provided to the maximum spectrum of patients' contexts and natural settings that can be achieved in and around the hospital setting. Although patients were exposed to several movements, it seems that variation of the exposure context also help explain why both exposures are successful in the generalization of extinction. Finally, based on results of research on experimental manipulations which indicate that lower fear at completion of exposure does not predict better outcomes overall (e.g. Farchione, 2002), the protocol of GEXP does not strive for a fear reduction of 100% from baseline during one exposure session. Certainly during the first eight exposure sessions a fear-reduction of 50% was experienced as successful. Thus, whereas reported fear and dysfunctional beliefs generally declined within an exposure session (although not always), there is good evidence to indicate that this decline was indicative of learning or of long-lasting improvement.

Where do we go from here?

Despite the success of GEXP in chronic pain patients who report high levels of pain-related fear there is still uncertainty about the basic principles that underlie it. Therefore, there is a need for more theory-based research. Studies focusing on expectancies, context, and neurocognitive processes might shed more light on the mechanisms underlying associations between pain-related fear and chronic pain.

Expectancies

Expectancies for the likelihood of aversive events are central to human fear conditioning (e.g. Craske et al., 2008). In chronic pain for example, propositional knowledge about the association between two stimuli, such as a specific activity and/or movement (CS) and subsequent pain or pain increase (US), as a potential sign of injury, (e.g. Lovibond & Shanks, 2002; Ohman & Mineka, 2001), is considered a strong correlate of conditioned responding. As already suggested, expected occurrence of the US (pain) is violated during GEXP. During GEXP, a mismatch between the expectancy of negative consequences of a certain activity and/or movement and the

absence of these consequences occurs. There probably are a number of ways of violating expectancies for pain (US). In the view of the studies in this thesis it seems that this may extend to the role of cognitive techniques applied within GEXP, which aim to shift expectancies for aversive events through logical empiricism. Future research should explicitly examine the role of cognitive techniques and which misconceptions are corrected during GEXP in order to fully understand what has been learned or has not been learned. Furthermore, research to durations or frequencies of unreinforced exposure to certain activities and/or movements that surpass the rate at which aversive events are expected to occur is warranted. It might be worthwhile to manipulate the duration of the GEXP trials relative to violation of fear-based expectancies.

Safety behavior

Should we wean safety signals and safety behaviors during GEXP? A number of studies have supported the hypothesis that safety behaviours are interfering with the benefits of exposure therapy (e.g., Sloan & Telch, 2002). Hence, by relying on safety behavior, anxious pain patients might be unable to obtain disconfirmatory evidence related to their unrealistic beliefs about certain pain stimuli. Indeed, they might conclude that their own actions (i.e., the safety behavior itself) prevent feared outcomes. In the context of GEXP, such strategies might thus inhibit the process of adaptive cognitive change about pain and related physiological signals. Tang and colleagues (2007) were the first who examined the use of safety-seeking behaviors (SSBs) in chronic low back pain patients. By exposing participants to pain-provoking situations (such as lifting) these authors identified a wide range of SSBs, particularly in patients with high health anxiety, which continued throughout the time the patient remained in a feared situation. Based on their findings Tang et al. (2007) suggested that SSB is distinct from overt pain behavior and may be a defining characteristic of chronic pain patients reporting high levels of health anxiety. Further, the study of Tang et al. (2007) also showed that the use of SSB was more strongly correlated with the presence of catastrophic thoughts during pain-provoking tasks, whereas the display of overt pain behavior was more strongly correlated with the level of pain experienced during these tasks. It is hypothesized that pain patients who catastrophize about physical activity, in that it will cause pain/(re)injury, will form SSBs, thereby prevent the pain patients from disconfirming their beliefs about danger from physical activities. Clinically, this may have important implications to the treatment of chronic pain patients in whom health anxiety is an important factor of their behavior. There is a need to look beyond communicative pain behavior and total avoidance of activities and movements as target for interventions (Tang et al., 2007). The use of behavioral experiments to challenge maladaptive thoughts and beliefs is emphasized by cognitive-behavioral theories of anxiety disorders (e.g.

Salkovskis et al., 2003). Well, as described behavioral experiments form part of GEXP. It seems therefore interesting to examine whether GEXP has the same results without the addition of behavioral experiments.

In addition to research on the role of safety behavior in exposure, a recent discussion dealt with the distinction between safety behavior and adaptive coping strategies (Thwaites & Freeston, 2005). Both strategies are aimed at reducing fear but are not intended to avoid catastrophic outcomes. Despite the theoretical distinction of safety behavior and coping, in clinical practice it is often difficult to differentiate between them. Differences can only be determined after evaluating a patient's intention for their use, their perceived function in a specific context, and the impact on catastrophizing. Depending on the feared consequences it seems possible that the same behavior functions both as safety mechanism and a coping strategy. For instance, a component of GEXP, the hierarchy of feared activities, may be perceived by some pain patients as a form of controlling pain and related physiological symptoms, leading them to fear situations in which they fail at control pain and related symptoms. On the other hand, it can also lead to greater perceived control, less fear during GEXP, and might increase patients' motivation at the start of GEXP to expose themselves to feared activities and/or movements. Furthermore, related research suggests that safety behavior promotes adaptive cognitive change (Rachman, 1993).

Based on the above mentioned findings there is a strong need for greater understanding of possible positive and negative consequences of safety behavior and the role of behavioral experiments in fearful pain patients. Is it only the perceived availability of safety behaviors that has a negative effect on fear reduction or is their use necessary? Is moving toward safety behavior during GEXP, rather than away from it, more effective in reducing avoidance behaviors? Do safety behaviors aid to modify catastrophic beliefs because of the fact that pain patients do not misattribute their success to external factors? What is the role of behavioral experiments rather than exposure to challenge catastrophic thoughts and beliefs? Does this allow patients to engage with the process of change behavior? Is there influence of duration to perform a pain-provoking task required to avoid ceiling effects? Most research to safety behavior is done in a laboratory setting by the use of a carefully standardized procedure: how is it in the "real world" (e.g. in patient's home/work situation)? In sum, there still are many questions about the use of safety behaviors of which the answers have important implications for GEXP.

Random GEXP

The generalization study in this thesis showed that exposure to multiple as well as 'only' single activities leads to generalization. Despite variability also random exposure is assumed to result in generalization (Schmidt & Bjork, 1992). In a random condition, patients practiced exposure to feared activities and/or movements in random order, which means that GEXP occurs with disregard of the fear hierarchy. Examining the effects of GEXP based on random GEXP compared to a so-called blocked GEXP in which the pain patient will be exposed to a certain feared activity repeatedly before moving to the next more feared activity might shed new light on this issue.

Spacing of GEXP sessions

Research has shown that temporally spaced exposure trials often result in a stronger acquisition-type of learning than temporally massed trials (e.g. Scharf et al., 2002). It seems that greater storage strength of memory is gained by partial forgetting between learning episodes, which in turn is presumed to slow the loss of the retrievable memory over time (Bjork & Bjork, 2003). Currently, the use of GEXP is outlined by a protocol which prescribed two exposure sessions in a week spread over 8 to 9 weeks. Because this schedule is not theoretically driven and GEXP with the protocol as it stands seems to be a successful treatment, both in the short and long run, one could wonder whether an expanding spaced schedule of progressively longer intervals between GEXP sessions or consecutive sessions might have any influence on the outcome of GEXP. In addition, it is important to study this topic in different varieties of pain complaints.

Offsetting context effects

Despite no return of fear was found in the generalization study as well as in the follow-up period in the other GEXP studies of this thesis and also in the early studies (Vlaeyen et al. 2001, 2002a, 2002b) there are still some questions that have to be answered. Is more return of fear found if re-testing occurred in the original fear acquisition context? For example, the environment of the hospital or proximity of medical facility may be a particularly meaningful context during GEXP. It remains to be determined which contexts play an important role in pain-related fear learning and extinction. Another question to investigate is whether pain-alone exposures also offset context-based renewal effects.

Neurobiological research

The majority of neurobiological research on fear learning and exposure has focussed on the amygdala, the prefrontal cortex (PFC) and the hippocampus (see Sotres-Bayon et al., 2006 for a review). The precise function of the amygdala is still unclear. Nevertheless it seems that this area plays a role in fear learning and is involved in extinction learning as well. The hippocampal formation seems to play a critical role in encoding contextual information, which is necessary to form an integrated memory of features of the context before conditioning can take place. Finally, the PFC seems responsible for executive control and decision making, and certain parts of the PFC (i.e., ventral medial) are responsible for emotional regulation, and, in particular, the ability to interpret emotional stimuli and change behavior accordingly (e.g. Craske et al., 2008).

Research to understand the neural mechanisms of GEXP, and emotional regulation during GEXP in particular, is hardly implemented. It seems interesting to understand how the PFC, amygdala and hippocampus interact to fully encode the extinction memory in fearful pain patients and which exact nature role the PFC and amygdala play in fear extinction. Given the role of the PFC, behavioral methods for enhancing PFC throughout GEXP may also prove to be a useful direction for research. If cognitive restructuring enhances the benefits of GEXP alone, it is quite conceivable that this may be done by activation of the PFC. Further, it would be of interest to establish the role of PFC activation in linguistic processing and typical cognitive restructuring and the connection of such activation to the development of new, inhibitory associations and expectancies.

Conclusions

This dissertation presented some studies to further explore the utility of GEXP. It has been shown that the application of GEXP has considerable promise in the treatment of pain patients who have a clearly articulated pain-related fear. The effects of GEXP generalized from chronic low back pain to other pain problems such as complex regional pain syndrome and posttraumatic neck pain. Significant advances have been made in understanding the behavioral and cognitive mechanisms involved in GEXP and how these mechanisms enhances generalization. Hopefully this work will contribute to better care for patients with chronic pain for who relatively few evidence-based treatment options exist.

Nederlandse samenvatting (Dutch summary)

Wanneer traditionele en biomedische behandelingen niet het beoogde resultaat opleveren, worden pijnpatiënten vaak doorverwezen naar revalidatiecentra. De behandelingen binnen deze centra zijn in het algemeen interdisciplinair en gebaseerd op bio-psycho-sociale en gedragsmatige revalidatie modellen. Deze modellen gaan ervan uit dat de ervaren beperkingen niet alleen bepaald worden door de onderliggende pathologie, maar ook door cognitieve factoren (b.v. het denken in catastrofes), gedragsmatige (b.v. het vermijden van bepaalde activiteiten), emotionele (b.v. sombere stemming) en sociale (b.v. algemene opvattingen over ziekte en gezondheid). Methoden die tijdens de behandeling aan bod komen zijn afkomstig uit de beginselen van de operante conditionering (observeerbaar pijngedrag zoals inactiviteit dient de focus van behandeling te zijn) en de cognitieve psychologie (focus ligt op de rol van attributies en verwachtingen, gevoel van controle en probleemoplossingvaardigheden). Onderzoek naar cognitief-gedragsmatige behandelingen laat wisselende resultaten zien. Dientengevolge wordt gesuggereerd om behandelingen nog beter af te stemmen op specifieke kenmerken van de patiënt. In de afgelopen jaren heeft cognitief-gedragsmatig pijnonderzoek zich dan ook gericht op mechanismen die een rol spelen bij de ontwikkeling van een acuut naar een chronisch pijnprobleem. Een aantal studies hebben laten zien dat aan pijn gerelateerde angst een van de sterkste voorspellers is voor de waargenomen variatie in fysieke prestaties bij pijnpatiënten.

Omdat pijngerelateerde angst een substantiële bijdrage levert aan het in stand houden van chronische pijn, is het een belangrijk doelwit binnen de behandeling. Sterker nog, verschillende studies hebben laten zien dat een exposure in vivo behandeling (GEXP) een effectieve behandeling is bij chronische lage rugpijn patiënten die een hoge mate van aan pijn gerelateerde angst rapporteren. Echter, de resultaten van deze studies en de complexiteit van GEXP hebben ook extra vragen opgevoerd. Bijvoorbeeld, welke behandelcomponenten maken GEXP al dan niet succesvol? Wat wordt eigenlijk geleerd tijdens GEXP? Is het uitdoven van pijngerelateerde angst te generaliseren naar andere bewegingen en activiteiten die niet zijn opgenomen in de GEXP? Is GEXP ook toe te passen bij pijnpatiënten met waarneembare weefselpathologie zoals neuropathische pijn? Kortom, antwoorden op deze vragen kunnen bijdragen aan het optimaliseren van GEXP bij pijngerelateerde angst. Het doel van dit proefschrift is om de toepassing van GEXP verder te onderzoeken door na te gaan 1) of GEXP, naast chronische rugpijn, ook positieve effecten oplevert bij andere pijnproblemen, zoals Complex Regionaal Pijn Syndroom en post-traumatische nekpijn, 2) wat de bijdrage is van specifieke behandelcomponenten in het resultaat van GEXP, en 3) of blootstelling aan meerdere stimuli generalisatie verbetert na afloop van GEXP.

In **hoofdstuk 1**, de inleiding van dit proefschrift, wordt allereerst stilgestaan bij het concept pijn. Pijn is een multidimensionele ervaring, die zowel een sensorische-

discriminatieve dimensie (b.v. de locatie, duur en intensiteit van de pijn) als affectief-motivationele dimensie heeft (b.v. de onaangenaamheden van pijn en angst voor pijn) bevat, en geen één-op-één relatie heeft met de mate van weefselbeschadiging. Er bestaat grote variabiliteit met betrekking tot de intensiteit van de ervaren pijn tussen individuen. Maar één individu kan pijn variëren afhankelijk van de context waarin het individu zich bevindt. Bovendien, wanneer de pijn aanhoudt en chronisch wordt lijken affectief-motivationele aspecten meer op de voorgrond te treden, terwijl de sensorische een geringere rol spelen bij de pijnervaring. Vervolgens wordt ingegaan op de rol van pijngerelateerde angst als verklaring waarom acute pijnpatiënten een chronisch pijnprobleem met de daarbij horende beperkingen kunnen ontwikkelen. Klassieke of Pavlovianse conditionering wordt van oudsher beschouwd als model voor de acquisitie van angst. Dit betekent dat een van oorsprong neutrale stimulus wordt gekoppeld met een biologisch relevante en bedreigende stimulus of situatie. Helaas is er weinig onderzoek gedaan naar de rol van klassieke conditionering in de ontwikkeling van pijn-gerelateerde angst. Het is echter waarschijnlijk dat een acute episode van ernstige pijn of andere lichamelijke sensaties wordt gezien als een teken van schade (ongeconditioneerde stimulus: US) en een onschuldige activiteit of beweging (geconditioneerde stimulus: CS) hieraan wordt gerelateerd. Het resultaat van dit leerproces is dat propositionele kennis over de relatie tussen de twee stimuli (de beweging met de toegenomen pijn als teken voor schade) wordt opgeslagen in het geheugen. Wanneer het subject wordt blootgesteld aan dezelfde soort van beweging, zal deze beweging de associatie met de toename van pijn activeren, wat resulteert in het uitlokken van een geconditioneerde respons (CR). Zelfs meer dan het oproepen van een herinnering, zorgt dit leerproces ervoor dat de betreffende beweging resulteert in het activeren van een actieve verwachting, namelijk die van een bedreigende gebeurtenis. Herhaling van het leerproces zorgt er ook voor dat de beweging een goede voorspeller wordt van toenemende pijn als teken van schade: 'Wanneer ik mijn vierjarig kind optil, dan ervaar ik onmiddellijk meer pijn in mijn rug wat duidelijk aangeeft dat mijn wervels versleten zijn' en 'Als ik mijn kind niet optil, dan zal de pijn in mijn rug niet toenemen, hetgeen betekent dat ik mijn wervels niet nog meer ga beschadigen'. Het subject legt niet alleen een verband tussen twee gebeurtenissen (associatief leren), maar leert ook dat de ene gebeurtenis de andere voorspelt (verwachtingsleren). Verwachtingsleren resulteert uiteindelijk in generalisatie van angst voor activiteiten, bewegingen en/of situaties vergelijkbaar met de onschadelijke beweging die de pijn heeft uitgelokt. De nieuwe en bedreigende betekenis van een oorspronkelijk neutrale beweging zorgt ervoor dat het subject zijn gedrag zal veranderen. Meer en meer activiteiten, bewegingen en/of activiteiten zullen worden vermeden. Pijngerelateerde angst kan zich ontwikkelen op minstens drie verschillende manieren: directe ervaringen (bijvoorbeeld een specifieke beweging verhoogt de pijn of de zwelling van de gebruikte arm); verbale informatie (bijvoorbeeld een arts die aan-

geeft dat er spraken is van artrose); of het observeren van anderen (bijvoorbeeld een vriend zittend in een rolstoel vanwege dezelfde pijnklachten of niet in staat is om te werken). Naast vermijding en ontsnappingsgedrag en verhoogde pijnervaring is pijngerelateerde angst gerelateerd aan denken in catastrofes over pijn, hypervigilantie, functionele beperkingen, veranderingen op centraal niveau, motorische abnormaliteiten, en depressiviteit. Exposure lijkt een geschikte behandeling. Het wordt gezien als een proces waarbij de patiënt tijdens een bepaalde periode herhaaldelijk wordt blootgesteld aan bedreigende situaties terwijl aversieve consequenties uitblijven. Dit proces wordt ook wel extinctie genoemd. Exinctie verwijst naar een zich herhalende presentatie van een geconditioneerde stimulus (CS: bijvoorbeeld een onschuldige activiteit) in de afwezigheid van de ongeconditioneerde stimulus (US: bijvoorbeeld een pijnproducerende of angstopwekkende stimulus) waarmee de CS voorheen was gekoppeld. Onderzoek heeft laten zien dat extinctie niet leidt tot het uitdoven van de angst en dat het veranderen van de context waarin extinctie heeft plaatsgevonden en het aanbieden van een onverwachte US ervaring na afloop van extinctie kan leiden tot een gedeeltelijk herstel van de ogenschijnlijk gedoofde angstreacties. Exinctie in wisselende contexten en herhaling lijkt in dit opzicht belangrijk te zijn. Bovendien blijkt dat cognitieve processen die disfunctionele overtuigingen beïnvloeden onderdeel uitmaken van de exposure therapie.

Voor pijnpatiënten die een hoge mate van pijngerelateerde vrees rapporteren is een 'graded exposure in vivo' (GEXP) ontwikkeld om extinctie van aan pijn gerelateerde angst te bewerkstelligen. Tijdens GEXP wordt de patiënt tijdens een bepaalde periode herhaaldelijk wordt blootgesteld aan bedreigende situaties. GEXP is zeer gestructureerd, geprotocolleerd, op maat gesneden, en streeft naar een normaal patroon van het dagelijks functioneren, met inbegrip van volledige terugkeer naar het werk. Zowel experimentele single-case studies als gerandomiseerde gecontroleerde studies (RCT) hebben aangetoond dat GEXP effectief is in het verminderen van functionele beperkingen bij patiënten met chronische lage rugpijn. Echter, bij twee RCT's was deze vermindering niet statistisch significant ten opzichte van een controle groep die op een wachtlijst stonden, gebruikelijke therapie (contact met een huisarts, medicatie, fysiotherapie) aangeboden kregen, of deelnamen aan een programma waarin stapsgewijs activiteiten werden opgebouwd. Over het geheel genomen is een van de meest opvallende kenmerken in deze studies het genoemde belang van de educatieve component van de exposure behandeling. Tijdens de educatie wordt het vrees-vermijdings-model geïllustreerd en uitgelegd. Ook wordt beschreven dat het belangrijk is om tijdens de exposure verschillende angstopwekkende activiteiten aan te bieden en dat therapeuten over de benodigde competenties beschikken. Tot slot, de resultaten van de single-case studies, alsook die van de RCT's, zijn hoopvol met betrekking tot generalisatie van extinctie.

Hoofdstuk 2 van dit proefschrift is gericht op de rol van pijngerelateerde angst bij patiënten met een Complex Regionaal Pijn Syndroom type I (CRPS-I), ook wel post-traumatische dystrofie genoemd. Twee studies worden gepresenteerd. Studie I omvat een steekproef van patiënten met een (sub)acute CRPS-I die zijn verwezen naar een poliklinische pijnpoli. In Studie II zijn patiënten met chronische CRPS-I en die lid zijn van de Nederlandse patiëntenvereniging uitgenodigd om deel te nemen aan een onderzoek. De resultaten van Studie I laten zien dat de hevigheid van de pijn, maar niet pijngerelateerde angst zoals gemeten met de Tampa Schaal voor Kinesiofobie (TSK), gerelateerd is aan de mate van functionele beperkingen bij een (sub)acute CRPS-I. Deze resultaten zijn niet consistent met eerder onderzoek bij patiënten met pijn aan het bewegingsapparaat waarbij een hoge TSK-score wel gerelateerd was aan de mate van functionele beperkingen, en zelfs meer nog dan de pijn zelf. Hoewel er een gebrek is aan consensus tussen onderzoekers, wordt CRPS-I gezien als een neuropathisch pijnsyndroom. Daarom is verondersteld dat de TSK niet gevoelig genoeg is om de mate van pijngerelateerde angst te meten, en is in Studie II ook een instrument gebruikt die bestaat uit foto's van dagelijkse activiteiten (PHODA) om pijngerelateerde angst te meten. De resultaten van Studie II laten zien dat bij patiënten met een chronische CRPS-I, naast de hevigheid van de pijn, ook de aan pijn gerelateerde angst, gemeten met de PHODA, een significante voorspeller is voor de mate van functionele beperkingen. Hoewel replicatie studies noodzakelijk zijn, lijkt het gerechtvaardigd om te concluderen dat de rol van pijngerelateerde angst een veelbelovende onderzoeksrichting is naar het begrijpen van de ervaren functionele beperkingen bij CRPS-I.

Hoofdstuk 3 en 4 beschrijven een tweetal studies waarin door middel van single-case experimenten met herhaalde metingen de effectiviteit van GEXP is onderzocht bij patiënten met posttraumatische nekpijn (PTNP) en CRPS-I. Patiënten die deelnamen aan de studie rapporteerden een hoge mate van pijngerelateerde angst. In de PTNP studie hebben patiënten zowel een GEXP alsook een operant 'graded activity' (OPE) programma doorlopen. Het doel van OPE is gezond gedrag bevorderen en pijngedrag te verminderen. Er wordt vanuit gegaan dat inactiviteit (pijngedrag) leidt tot een verminderde belastbaarheid, welke pijn bevordert, en dat het verhogen van het activiteitenniveau en de spiersterkte in de toekomst waarschijnlijk zal leiden tot minder beperkingen. De volgorde waarin GEXP en OPE werd aangeboden gebeurde op basis van toeval. Door gebruik te maken van dagboekjes hebben beide studies laten zien dat tijdens GEXP er niet alleen een significante vermindering plaatsvindt van pijngerelateerde angst en het denken in catastrofes over pijn, maar ook voor wat betreft pijnintensiteit. Tevens rapporteren alle patiënten tijdens GEXP doelen te kunnen bereiken die betrekking hebben op de uitvoering van activiteiten die bij aanvang van de studies als onmogelijk werden verondersteld. Gestandaardiseerde vragenlijsten over pijngerelateerde angst, pijnintensiteit en functionele beperkin-

gen, die voorafgaande en na afloop van iedere interventie werden afgenomen laten alleen na afloop van GEXP een significante afname zien. Om het niveau van dagelijkse fysieke activiteit te kwantificeren werd door PTNP patiënten tijdens deze perioden ook een ambulante bewegingsmeter gedragen. Een significante toename van de dagelijkse fysieke activiteit was wederom alleen te zien na afloop van GEXP. Tenslotte, het meest opvallende resultaat was dat fysiologische verschijnselen en symptomen, zoals abnormale gevoeligheid voor prikkeling van de zintuigen, oedeem, veranderde lichaamskleur en temperatuur, en een verstoorde zweetsecretie, die verband houden met CRPS positief werden beïnvloed door GEXP. Tijdens een follow-up meting van 6 maanden bleken alle hierboven beschreven positieve resultaten, als gevolg van GEXP, nog steeds aanwezig te zijn. Beide studies ondersteunen de effectiviteit van GEXP bij patiënten met PTNP en CRPS-I die een hoge mate van pijngerelateerde angst rapporteren.

Klinisch onderzoek, dat mede heeft geleid tot de vraagstellingen binnen dit proefschrift, heeft laten zien dat bij chronische lage rugpijn patiënten vrij snel na de start van het GEXP programma een abrupte afname van pijngerelateerde angsten en cognities plaatsvindt. Deze abrupte veranderingen zijn meer een kenmerk van inzichtelijk leren in plaats van de gebruikelijke leermethode van vallen en opstaan. Als het GEXP protocol is gevolgd, zou het dus zo kunnen zijn dat het educatieve deel aan het begin van GEXP heeft bijgedragen tot dit inzicht. **Hoofdstuk 5** van dit proefschrift beschrijft een studie waarin de bijdrage van de educatie aan het verminderen van pijngerelateerde angst, en de daaraan verbonden beperkingen in fysiek functioneren, bij chronische lage rugpijn patiënten is onderzocht. Na een periode waarin geen enkele behandeling is gevolgd, kregen alle patiënten het educatieve deel van de GEXP aangeboden, gevolgd door wederom een behandelvrije periode. Patiënten werden vervolgens willekeurig toegewezen aan hetzij GEXP of een gedragsmatige oefentherapie (OPE). Ook nu weer werd een dagboekje gebruikt om dagelijkse veranderingen van pijnintensiteit, pijngerelateerde angst, het denken in catastrofes over pijn en de moeilijkheid om een bepaalde activiteit uit te voeren te meten. Tevens werd voorafgaand en na afloop van iedere interventie en tijdens een 6-maanden follow-up gestandaardiseerde vragenlijsten afgenomen om pijngerelateerde angst, gevoeligheid voor pijn, pijnintensiteit en ervaren beperkingen als gevolg van de pijn te meten, en droegen de patiënten gedurende één week een ambulante bewegingsmeter. De resultaten van de dagelijkse metingen laten zien dat pijngerelateerde angst inderdaad positief werd beïnvloed door de educatie. Echter, het uitvoeren van relevante dagelijkse activiteiten werd niet beïnvloed door de educatie, maar verbeterde alleen onder invloed van GEXP. Ook tijdens de 6-maanden follow-up werden deze verbeteringen alleen gevonden bij patiënten die een GEXP hadden gevolgd, en rapporteerde deze groep zelfs een significante afname in pijnintensiteit.

Ondanks het succes van GEXP bij chronische pijn is het nog de vraag of extinctie generaliseert naar nieuwe bedreigende activiteiten. Uit dierexperimenteel onderzoek naar de terugkeer van angst is gebleken dat extinctie niet betekent afleren betekent. Het lijkt erop dat de gedoofde angstreactie na een tijdje weer spontaan kan ontstaan, of opnieuw kan optreden bij confrontatie met een nieuwe CS-US gebeurtenis of een onverwachte US. Tevens lijkt extinctie ook context gevoelig. Exposure onderzoek bij lage rugpijn patiënten heeft laten zien dat wat is geleerd tijdens extinctie niet noodzakelijkerwijs generaliseert naar andere situaties, zelfs niet wanneer extinctie plaatsvindt in een situatie waarin de oorspronkelijke angst is ontstaan. **Hoofdstuk 6** van dit proefschrift beschrijft een studie met als primaire doel een eerdere studie te repliceren waarin gevonden werd dat exposure aan meerdere stimuli en/of contexten generalisatie bevordert. Door gebruik te maken van een single-case experimenteel design werd onderzocht of de effecten van GEXP bij angstige CRPS-I patiënten generaliseren naar bedreigende activiteiten waaraan de patiënten tijdens GEXP niet zijn blootgesteld. Twee GEXP condities bestaande uit 15 sessies van één uur werden met elkaar vergeleken. Conditie I bestond uit een GEXP programma van minimaal 15 activiteiten waaraan patiënten slechts één keer werden blootgesteld en Conditie II uit 3 activiteiten waaraan patiënten vijf maal werden blootgesteld. In beide condities werd generalisatie van extinctie getest door patiënten na een succesvolle GEXP bloot te stellen aan een nieuwe activiteit. De veronderstelling was dat generalisatie van extinctie wordt bevorderd door de conditie waarin de meerdere activiteiten werden aangeboden. In tegenstelling tot wat werd verwacht presteerden de patiënten uit beide condities even goed tijdens de test exposure. Bij alle patiënten was sprake van generalisatie naar een nieuwe activiteit direct na afloop van GEXP en tijdens een 6-maanden follow-up. Over het geheel genomen lijkt het erop dat, ongeacht de aard van GEXP, extinctie generaliseert naar nieuwe bedreigende activiteiten.

Tenslotte worden in **hoofdstuk 7** allereerst de bevindingen van dit proefschrift samengevat en vervolgens ter discussie gesteld. De studies in dit proefschrift hebben aangetoond dat GEXP een veelbelovende behandeling is voor chronische pijnpatiënten die een hoge mate van pijngerelateerde angst rapporteren. De effecten van GEXP generaliseren van chronische lage rugpijn naar andere pijnproblemen zoals CRPS-I en PTNP. Aanzienlijke vooruitgang is geboekt in het begrijpen van de gedragsmatige en cognitieve mechanismen die betrokken zijn bij GEXP en hoe deze mechanismen generalisatie van extinctie versterken. Desondanks blijven er nog steeds onduidelijkheden bestaan over de cognitieve processen die ten grondslag liggen aan het succes van GEXP. Er is daarom behoefte aan meer theoretisch gericht onderzoek. Studies gericht op verwachtingen (bijvoorbeeld, voorgenomen kennis over het verband tussen een specifieke activiteit en de daaropvolgende pijn als

potentieel teken van schade), het wel of niet toepassen van veiligheidsgedrag tijdens GEXP, willekeurige exposure (GEXP wordt aangeboden zonder acht te slaan op de angsthiërarchie), het leereffect van tijdelijk gespreide en opeenvolgende exposuresessies, het neutraliseren van de context (bijvoorbeeld, het gegeven dat GEXP plaatsvindt in het ziekenhuis kan een belangrijke rol spelen), en neuro-cognitieve processen werpen misschien meer licht op de mechanismen die ten grondslag liggen aan de associaties tussen pijngerelateerde angst en chronische pijn.